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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,072	10/14/2005	Ralf-Holger Voss	BB-140	1890

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
09/25/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/529,072	VOSS ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12-19 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12-19 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9-8-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-8-09 has been entered.

Applicants' amendment filed 9-8-09 has been entered. Claims 20-23, 27 and 28 have been canceled. Claims 31-33 have been added. Claims 1-9, 12-19 and 29-33 are pending and under consideration.

Claim Objections

2. Claim 1 is objected to because of the following informalities: The phrase "in (a) joint or separate mutagenesis-vector system(s)" in lines 11-12 appears to be a typographical error. The term "(a)" seems to mean "a". Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3-6, 17, 18 and 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "said mutagenizing comprising exchanging Gly192" in lines 5-6 of claim 32 is vague and renders the claim indefinite. The term "comprising" is an open language that implies some other element is intended. It is unclear what other "mutagenizing" is intended in the claim.

The phrase "said mutagenizing comprising exchanging Arg208" in lines 8-9 of claim 32 is vague and renders the claim indefinite. The term "comprising" is an open language that implies some other element is intended. It is unclear what other "mutagenizing" is intended in the claim.

The term "and/or" in line 4 of claim 3 is vague and renders the claim indefinite. It is unclear what is intended. Changing the term "and/or" to "…or…or both" would be remedial. Claims 4 and 5 depend from claim 3.

The phrase "additional (functional) domains" in line 3 of claim 6 is vague and renders the claim indefinite. It is unclear whether the term "(functional)" is intended in the claim or not. Removing the parenthesis would be remedial.

The phrase "alternative domains" in line 3 of claim 6 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "alternative domains".

The term "MDM2" in claim 17 is vague and renders the claim indefinite. The term "MDM2" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Claim 18 depends from claim 17.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-9, 12-19 and 29-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a TCR complex wherein the alpha- and beta-chains of an MDM2(81-88)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain and the Arg208 of the constant region of the beta-chain are exchanged by Arg 192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain, does not reasonably provide enablement for a method, in vitro or in vivo, for producing any other hetrodimeric specific wild-type or chimeric TCR having any antigen specificity, wherein glycine, serine, threonine, valine, or alanine is introduced after the mutagenesis of the DNA molecule that introduces the sterically recessed group including Arg208, and glutamine, glutamic acid, alpha-methylvaline, histidine, hydroxylysine, tryptophan, lysine, arginine, phenylalanine or tyrosine is introduced after the mutagenesis of the DNA molecule that introduces the sterically projecting group including Gly192. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed

invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims read on a method, in vitro or in vivo, for producing any other hetrodimeric specific wild-type or chimeric TCR having any antigen specificity, wherein glycine, serine, threonine, valine, or alanine is introduced after the mutagenesis of the DNA molecule that introduces the sterically recessed group including Arg208, and glutamine, glutamic acid, alpha-methylvaline, histidine, hydroxylysine, tryptophan, lysine, arginine, phenylalanine or tyrosine is introduced after the mutagenesis of the DNA molecule that introduces the sterically projecting group including Gly192. Claim 2 specifies subcloning of the mutated fragments into a suitable transfection vector system, transfection or transduction of at least two of the mutated fragments into a mutant TCR-deficient T cell. Claims 3 and 4 specify in vitro or in vivo translation of at least tow of the mutant-fragment and paring of the heterodimeric specific first/second-chain TCR

and introduction of the mutated specific first/second-chain TCR into a T cell. Claim 5 specifies the introduction takes place by liposome-transfer. Claim 6 specifies the TCR is an alpha/beta TCR, a gamma/delta TCR, a humanized or partially humanized TCR. Claim 7 specifies the amino acids as introduced after the mutagenesis of the DNA-molecules are further chemically modified. Claims 13 and 14 specify the corresponding interacting surfaces are located in the variable domains and constant domains of the TCR-chains, respectively. Claim 15 specifies the domains to be mutated are mammalian domains. Claim 17 specifies the alpha- and beta- chains of an MDM2(81-88)-specific TCR are used, and Gly192Arg and Arg208Gly are introduced. Claim 18 specifies additional positions are modified in the chains. Claim 19 specifies a retroviral vector is used as a transfection system. Claims 29 and 30 specify the mutagenesis of the DNA molecules is in a TCR-ecto-domain and constant domain, respectively. Claim 31 specifies the method is performed in vitro.

Nature of Invention:

The instant invention relates to a method for producing hetrodimeric specific wild type or chimeric T-cell receptor (TCR).

Breadth of Claims and Guidance Provided By the Inventor

The scope instant claims encompasses method for producing various hetrodimeric specific wild-type or chimeric TCR with any antigen specificity, wherein various domains, including constant domain, variable domain and ecto-domain etc., of the TCR-complex has been modified by the recited mutagenesis. The specification teaches a method for making the TCR complex wherein the alpha- and beta-chains of an MDM2(81-88)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain

and the Arg208 of the constant region of the beta-chain are exchanged by Arg 192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain. Besides the MDM2(81-88)-specific TCR the specification as filed fails to disclose any other recombinant product that would enable one skill art to practice the invention as claimed.

State of Art and Predictability:

The state of the art at the time of filing was such that the TCR is the most intricate membrane receptor structures known in the art, wherein any mutation in the TCR-complex would cause unintentional conformational changes rendering the scope of invention as claimed highly unpredictable. The TCR assembly is directed by unique polar contacts within the transmembrane domains, whereas extracellular contacts can contribute to stability and specificity. There is a segregation of functions among the subunits: the ligand-binding subunits have no intrinsic signaling capacity, signals are communicated instead via non-covalently associated, dimeric signaling modules that have cytoplasmic phosphorylation motifs. The functions of the domains within each subunit are topologically segregated: whereas the extracellular domains bind ligands and the cytoplasmic domains recruit signaling molecules, the sequences that direct assembly of signaling modules with their receptors reside primarily within the membrane-embedded and membrane-proximal segments. The specific mechanism of signal initiation has yet to be definitively determined for any of these receptor systems, and the concepts of the molecular architecture of activating immune receptor complexes have important consequences for how one envision signals to be propagated across the membrane. Therefore, understanding the structure and mechanics of activating immune receptors is crucial to the development of accurate models of any TCR functionality, especially in the context of the instant

invention as claimed. The studies reviewed here represent a significant advance in the mapping of structurally and functionally relevant molecular interactions within a group of receptor complexes that share a distinctive assembly mechanism and, consequently, a similar subunit arrangement. But what can these new and developing structural insights tell us about the mechanics of signal initiation through these important immune receptors as a group? As discussed in the cited art, the compartmentalization of sequence elements responsible for critical inter-subunit contacts is compatible with activation models involving major reorientations among extracellular and/or cytoplasmic domains. Therefore, only complete understanding of receptor triggering mechanisms would enable one skilled in the art to practice the invention as claimed. See Khuns et al IMMUNITY. 26:357-369, 2007, Khuns et al, IMMUNITY. 24(2):133-139, 2006. Call et al, NATURE REVIEWS IMMUNOLOGY 7:841-850,2007, Call et al MOL IMMUNOL. 40(18):1295-1305, 2004.

Further, the claims read on substituting or mutating various amino acid positions in numerous different TCRs derived from numerous organisms with recited amino acid residues. It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Davis, C. G., 1990 (The New Biologist, Vol. 2, No. 5, p. 410-419) reports that EGF repeats appears in an extraordinarily diverse group of

molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid contexts, i.e. different proteins.

In addition, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention and even same short stretch of amino acid sequence can show diverse biological functions while surrounded by different background amino acid sequences. Different amino acid substitutions or mutations in various TCRs can result in diverse TCR antigen specificities and its signaling functions, and the effect of the amino acid substitutions or mutations on the TCR antigen specificities and its signaling functions would be unpredictable at the time of the invention. Absent specific guidance, one skilled in the art at the time of the invention would not know whether the heterodimeric specific wild-type or chimeric TCR could still maintain (not impaired) its functionality and stability as claimed.

It should be noted that claims 32 and 33 read on exchanging Gly192 of the alpha-chain and Arg208 of the beta-chain of various TCRs derived from numerous different organisms with recited amino acid residues. Different TCRs derived from various organisms could have different amino acid sequences and it is not necessary that Glycine would be at amino acid position 192 of various alpha-chain and Arginine would be at amino acid position 208 of various beta-chain of TCRs. When Glycine is not at amino acid position 192 of alpha-chain and when Arginine is not at amino acid position 208 of beta-chain, one skilled in the art at the time of the invention would not be able to perform the claimed method to produce a T-cell expressing a T-cell receptor (TCR).

In addition, the scope of the claims 1-9, 12-19, 29 and 30 encompasses genetic modification of a cell in vivo, therefore the claims read on gene therapy in vivo. The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al., Sept. 1997

(Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Different promoters have different activity in stimulating gene expression in different cells in vivo and whether there is sufficient expression of the wild-type, chimeric or mutant polypeptide in the desired population of cells depends on what promoter is used.

Administration route plays a very important role in determining whether sufficient wild-type, chimeric or mutant polypeptide can be expressed and present at the target cells at various locations in vivo. The administration route includes direct administration to the target cells, oral administration, intraperitoneal injection, topical administration, intravenous administration, intramuscular injection, and subcutaneous administration etc. There are various barriers before a nucleic acid construct can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) reports that numerous factors complicate in vivo gene transfer with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material

within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced (e,g, bridging pages 81-82). Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). In addition, Thomas et al., 2003 (Nature Reviews/ Genetics, Vol. 4, p. 346-358) discusses the problem of viral vector in gene therapy. Thomas reports that "adenovirus vectors induce multiple components of the immune response: cytotoxic T-lymphocyte (CTL) responses can be elicited against viral gene products or "foreign" transgene products that are expressed by transduced cells, and the capsid itself--- in the absence of viral gene expression --- induces humoral virus-neutralizing antibody responses and potent cytokine-mediated inflammatory responses (e.g. p. 352, right column). Absent specific guidance, one skilled in the art at the time of the invention would not know how to produce a heterodimeric specific wild-type or chimeric T-cell receptor (TCR) in various locations of a subject by administering the claimed DNA molecules via various administration routes in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of skill which is high,

the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

Applicants argue that the scope of the claims does not encompass the modification of "any and all domains...of the TCR-complex" rather the claims indicate that a "surface" on a first and second chain are mutagenized for the introduction of sterically projecting and recessed groups into each respective polypeptide chain such that TCR functionality and stability is not impaired. A “surface” is the area of a TCR that interacts with a particular area of the second chain of the TCR, the crystal structure of the TCR has been resolved at 2.5Angstrom level and various “surfaces” that interact with one another were known at the time of the invention. Applicants further argue that the constant regions of alpha and beta-chains have a relatively high degree of sequence identity (amendment, p. 7-9). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph. Since the "surface" is the area of a TCR that interacts with a particular area of the second chain of the TCR, the "surface" can be anywhere in the first and second chains of the TCR, which includes extracellular, transmembrane and intracellular domains. Although the cited Garcia reference shows the 3D-structure of alpha-chain and beta-chain interaction of the TCR, there appears to be several interacting "surface" between those two chains, for example, Figures 2 and 4 of Garcia. Further, Garcia only shows one particular TCR complex. Different TCR complex having different amino acid sequences would have different interacting "surfaces" between the alpha-chain and beta-chain. The scope instant claims encompasses method for producing various hetrodimeric specific wild-type or

chimeric TCR with any antigen specificity, wherein various domains, including constant domain, variable domain and ecto-domain etc., of the TCR-complex has been modified by the recited mutagenesis. The claims are not limited to constant domain. The TCR is the most intricate membrane receptor structures known in the art, wherein any mutation in the TCR-complex would cause unintentional conformational changes rendering the scope of invention as claimed highly unpredictable. Different amino acid substitutions or mutations in various TCRs can result in diverse TCR antigen specificities and its signaling functions, and the effect of the amino acid substitutions or mutations on the TCR antigen specificities and its signaling functions would be unpredictable at the time of the invention. Whether or not the produced wild-type or chimeric TCR functionality and stability would not be impaired would be unpredictable at the time of the invention. Absent specific guidance, one skilled in the art at the time of the invention would not know whether the heterodimeric specific wild-type or chimeric TCR functionality and stability would not be impaired as claimed. It is also noted that claims 32 and 33 read on exchanging Gly192 of the alpha-chain and Arg208 of the beta-chain of various TCRs derived from numerous different organisms with recited amino acid residues. Different TCRs derived from various organisms could have different amino acid sequences and it is not necessary that Glycine would be at amino acid position 192 of various alpha-chain and Arginine would be at amino acid position 208 of various beta-chain of TCRs. When Glycine is not at amino acid position 192 of alpha-chain and when Arginine is not at amino acid position 208 of beta-chain, one skilled in the art at the time of the invention would not be able to perform the claimed method to produce a T-cell expressing a T-cell receptor (TCR).

Applicants argue that methods of delivering nucleic acids to target cells were known in the art and particular targeting agents and/or condensing agents need not be recited in the claims to satisfy the enablement requirements of section 112 and claim 5 indicates that nucleic acid are delivered, in vitro or in vivo, via liposome transfer (amendment, p. 9). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

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